CASE REPORT

Virus-associated haemophagocytic lymphohistiocytosis in a young Filipino man

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SUMMARY

Haemophagocytic lymphohistiocytosis (HLH) is a rare syndrome of pathological immune activation characterised by extreme inflammation. We present a case of a young Filipino man consulting for non-specific symptoms of fever, body malaise and weight loss. Prominent physical examination findings included gross pallor, cachexia and hepatosplenomegaly. Laboratory results revealed pancytopenia, while bone marrow examination revealed haemophagocytosis. Further workup for HLH showed hypertriglyceridaemia, hypofibrinogenaemia and hyperferritinaemia (fulfilling 6 of 8 diagnostic criteria). Exhaustive serological and haematological examinations showed chronic hepatitis B virus infection and past evidence of Epstein-Barr virus infection as possible triggers. The patient was started on antiviral therapy, high-dose steroids and chemotherapy. He initially improved, but eventually succumbed to severe fungal sepsis and pulmonary haemorrhage. An autopsy confirmed the diagnosis of HLH.

BACKGROUND

Haemophagocytic lymphohistiocytosis (HLH) is a rare syndrome of pathological immune activation characterised by clinical signs and symptoms of extreme inflammation.¹ This report aims to demonstrate the clinical and laboratory approach to treatment for patients suspected of having HLH, and to describe therapeutic approaches to the disease.

CASE PRESENTATION

A 21-year-old Filipino man presented at the emergency department, with a 1-month history of intermittent fever associated with body malaise, anorexia and weight loss. The review of symptoms and medical history were both unremarkable. There was history of neither recent travel nor wading in floodwaters; however, a brother had succumbed to severe leptospirosis 2 months prior. The patient was a smoker and drank occasionally, but had taken neither medications, health supplements nor illicit drugs. There was a history of unprotected sex with 10 women. On examination, the patient appeared malnourished and grossly pale; he was febrile at 38.0°C. Abdominal examination revealed hepatosplenomegaly. He had neither jaundice, lymphadenopathy nor skin rash. Preliminary laboratory tests showed pancytopenia with a low Reticulocyte Production Index (RPI) of 0.56 and a low absolute neutrophil count of 272 cells/mm³, mild hypokalaemia, indirect hyperbilirubinaemia, hypoalbuminaemia and elevated liver functions. Lactic dehydrogenase was high at 1790 U/L

(normal up to 500 U/L). Indirect and direct Coombs tests were negative, and the peripheral blood smear was likewise unremarkable. Coagulation profile, renal function tests and chest X-ray were all normal, while blood, urine and sputum cultures turned out negative. The patient was initially managed for febrile neutropaenia, and was started on empiric broad-spectrum antimicrobials and blood transfusion. Referrals to haematology and infectious disease services were made. Subsequently, bone marrow examination showed a hypercellular marrow with bizarre-looking cells (labelled as erythroid or reactive lymphocytes) and infiltration by haemophagocytes, suggesting the diagnosis of HLH.

INVESTIGATIONS

Chromosomal analysis and flow cytometry of marrow specimens were unremarkable. Further investigations showed hypertriglyceridaemia (357 mg/dL; normal <265 mg/dL), hyperferritinaemia (>1000 ng/mL; normal <500 ng/mL) and hypofibrinogenaemia (1.25 g/L; normal 1.5–4 g/L), thus fulfilling the criteria for the diagnosis of HLH. An exhaustive work up was then performed to look for a possible underlying cause. Autoimmune titres (antinuclear antibodies and rheumatoid factor) were negative, as was tuberculosis work up for stool, urine, sputum and bone marrow smears. Serologies for hepatitis A and C, HIV, syphilis and malaria were also negative. However, hepatitis B virus (HBV) surface and envelope antigens were positive, with DNA copies at 921 500 IU/mL, and there was also evidence of past Epstein-Barr virus (EBV) infection (EBV enzyme-linked fluorescent assay IgG 2.73 µ/mL; normal <0.271 µ/mL).

TREATMENT

As immunosuppressive treatment was contemplated, the patient was started on lamivudine due to the risk of a hepatitis flare. Chemotherapy was then initiated according to the recommendations of the HLH-94 protocol, consisting of dexamethasone 10 mg/m², etoposide 150 mg/m² and cyclosporine 200 mg.² As an expected side effect of the chemotherapy, serial blood count monitoring showed decreasing trends of all cell lines, hence granulocyte colony-stimulating factor was started.

OUTCOME AND FOLLOW-UP

During the course of his admission, the patient was transferred to the intensive care unit for close monitoring. On the 21st hospital day, he developed hospital-acquired pneumonia, necessitating a step

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up in antimicrobial therapy. Since he failed to respond to antibiotics alone after 3 days, empiric oral fluconazole was eventually added. However, his condition deteriorated rapidly and he ultimately succumbed to multiple organ failure and severe sepsis. Autopsy revealed haemothorax, bilateral haemorrhagic lung surfaces and hyphal elements compatible with *Aspergillus* species. Haemophagocytes were identified in the spleen, lymph nodes and bone marrow, consistent with the antemortem diagnosis of HLH.

DISCUSSION

HLH is a rare condition, with ~1.2 cases per million individuals per year.¹ The disease can either be primary, where genetic mutations in the cytolytic secretory pathway cause perforin-induced and granzyme-induced apoptosis in target cells;³ or secondary, with underlying conditions such as viral (29%) and other (20%) infections, malignancies (27%), rheumatological disorders (7%) and immunodeficiency syndromes (6%).⁴ Regardless of cause, HLH is characterised by defective cytotoxic cell function and uncontrolled macrophage activity, leading to excessive cytokine production, a dysregulated inflammatory response causing severe neutropaenia and immunodeficiency. Owing to non-specific clinical and laboratory findings, diagnosis is often difficult. The official diagnostic criteria established by the Histiocyte Society suggest a probable diagnosis when five of eight features (fever, splenomegaly, bicytopenia, hypertriglyceridaemia and/or hypofibrinogenaemia, haemophagocytosis, low/absent natural killer (NK) cell activity, hyperferritinaemia and high-soluble interleukin 2 (IL-2) receptor levels) are fulfilled. Diagnosis is confirmed by tissue demonstration of haemophagocytosis in the bone marrow, spleen or lymph nodes.⁵ HLH is a fatal disease, with long-term survival rates estimated to be as low as 4%. The median survival without treatment is estimated to be <2 months.⁶

We described a young man initially presenting with non-specific symptoms of fever, hepatosplenomegaly and pancytopenia. The differentials for febrile neutropaenia are varied and include infections, malignancies, iatrogenic causes, immune deficiencies, metabolic disorders, autoimmune disorders and congenital aetiologies. Further specific investigations for these aetiologies must be tailored according to careful history-taking

and a physical examination.⁷ Although a brother had recently died from leptospirosis, this condition was not entertained since the patient had no risk factors and his clinical course was not typical of the disease. Subsequently, the patient's triad of symptoms made us suspect an infiltrative disorder or bone marrow failure state. In his age group, the most common haematological malignancies include acute lymphocytic leukaemia and acute myelogenous leukaemia; another strong differential commonly seen in developing countries such as the Philippines, is tuberculosis of the bone marrow. These diseases, however, were not consistent with the bone marrow picture, which showed hypercellularity with marked haemophagocytosis.⁸ Further workup consequently showed hypertriglyceridaemia, hyperferritinaemia and hypofibrinogenaemia, confirming the diagnosis of HLH (fulfilling 6 of 8 diagnostic criteria, table 1). Supportive findings included hyperbilirubinaemia, which can be explained by tropism of activated histiocytes to the biliary tree; and a low RPI, consistent with ineffective erythropoiesis secondary to marrow infiltration by activated macrophages in HLH.⁹

We then investigated the possibility of an underlying cause for HLH. An autoimmune aetiology was ruled out as serology titres were negative. An exhaustive microbiological work up, meanwhile, showed chronic hepatitis B with high replicative status and past EBV infection; hence virus-associated HLH was entertained. This was consistent with a retrospective study, which revealed that among patients with HLH aged 15–29 years, infection was the most common aetiology (68%), with EBV accounting for half the cases.¹⁰ Another study on EBV-associated HLH stated that both new EBV infection and reactivation of latent infection can predispose individuals to HLH.¹¹ The mechanism is due to stimulation, generation and uncontrolled secretion of T cells and NK cells by the EBV-infected B cells, as well as unregulated generation of IL-2, interferon α and IL-6.¹² On the other hand, there are only two case reports describing the association of chronic active HBV infection and HLH—one due to isolated HBV infection, and the other from coexistent HBV and hepatitis C infection.^{13 14} In this patient, it was difficult to ascertain the specific aetiology for HLH (whether HBV or EBV), as both were possible triggers for disease development.

Treatment of HLH generally involves immunosuppressive agents, biological response modifiers, treatment of the inciting illness if secondary and stem cell transplantation. Being unable to afford a transplant, the patient was started on a combination of dexamethasone, etoposide and cyclosporine, since the HLH-94 study showed that a combination of the first two drugs possessed significantly better survival and sustained remission

Table 1 HLH-2004 diagnostic criteria and the criteria fulfilled by the patient

HLH-2004 Diagnostic criteria	Criteria fulfilled
The diagnosis of HLH can be established if 1 of either point below is fulfilled:	
1. A molecular diagnosis consistent with HLH is made	—
2. Diagnostic criteria for HLH are fulfilled (5 of 8 criteria below):	—
Fever	✓
Splenomegaly	✓
Cytopenias (affecting >2–3 lineages in the peripheral blood)	✓
Haemoglobin <90 g/L (in infants <4 weeks, haemoglobin ≤100 g/L), platelets <100×10 ⁹ /L, neutrophils <1.0×10 ⁹ /L	✓
Hypertriglyceridaemia and/or hypofibrinogenaemia; fasting triglycerides ≥3.0 mmol/L (ie, ≥265 mg/dL), fibrinogen ≤1.5 mg/L	✓
Haemophagocytosis in BM, spleen or lymph nodes	✓
Low or absent NK cell activity	—
Ferritin ≥500 µg/L	✓
Soluble CD25 ≥2400 µ/mL	—

BM, bone marrow; HLH, haemophagocytic lymphohistiocytosis; NK, natural killer.

Learning points

- ▶ Haemophagocytic lymphohistiocytosis (HLH) is a rare and fatal disease with non-specific clinical manifestations and vague laboratory findings.
- ▶ A presumptive diagnosis, which must not be missed, is made if at least five of eight diagnostic criteria are fulfilled, with the diagnosis confirmed by marrow examination.
- ▶ Reactivation of new and latent Epstein-Barr virus together with hepatitis B virus can trigger HLH.
- ▶ Despite well established treatment with high-dose steroids and chemotherapy, together with treatment of the inciting illness, the prognosis remains poor.

rates; in addition, administration of cyclosporine, in one study, appeared to increase efficacy especially in neutropaenic HLH cases.¹⁵ In the aforementioned HBV-associated case reports, both patients received cyclosporine and high-dose steroids; while in EBV-associated HLH, etoposide-based chemotherapy was proven to be effective compared to high-dose steroids alone or in combination with intravenous immunoglobulin.² Despite intensive treatment, however, the patient still succumbed to disease complications and severe sepsis. This was consistent with reports stating that use of the HLH-94 protocol merely afforded patients a median survival of 54% at 6.2 years. This high fatality rate emphasises the need for prompt diagnosis, constant vigilance and closer monitoring of patients with HLH.

Contributors JC wrote the draft of the manuscript and its revisions, while MGY edited the manuscript and gave final approval. Both the authors were involved in the care of the patient.

Competing interests None declared.

Patient consent Obtained.

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